



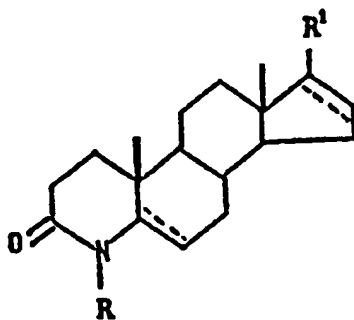
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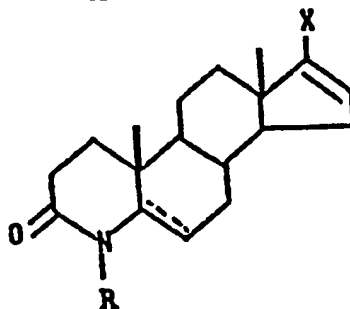
(54) Title: NOVEL PROCESS FOR PREPARING 17 β -SUBSTITUTED 4-AZAANDROSTANE DERIVATIVES

(57) Abstract

The invention relates to a novel process for preparing 17 β -substituted 4-azaandrostane derivatives of general formula (I) wherein R represents hydrogen or a C₁-alkyl group; R¹ represents a carboxamido group mono- or disubstituted by C₁-alkyl group(s); or a free carboxyl group; or a carboxyl group esterified with a C₁₋₃ alcohol; and the — bond line represents a single or double bond; as well as their salts. The process comprises reacting a 17-halogeno-4-azaandrostene derivative of general formula (II) wherein R and the — bond line are as defined above, and X is chlorine, bromine or iodine, with a primary or secondary alkylamine or a C₁₋₃ alcohol, in dimethylformamide or dimethylsulfoxide medium in the presence of a palladium(II) salt and phosphines or a palladium(II) complex and a tertiary amine base in carbon monoxide atmosphere at a temperature between 35 °C and 80 °C, then, if desired, transforming an obtained compound of general formula (I) to another compound of general formula (I) by hydrogenation, hydrolysis or salt forming reaction.



(I)



(II)

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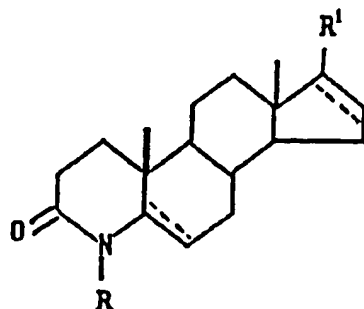
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NOVEL PROCESS FOR PREPARING 17 β -SUBSTITUTED
4-AZAANDROSTANE DERIVATIVES

5 This invention relates to a novel process for
preparing 17 β -substituted 4-azaandrostane derivatives
of general formula (I)

10

15



(I)

wherein

- R represents hydrogen or a C₁₋₃alkyl group;
- 20 R¹ represents a carboxamido group mono- or
disubstituted by straight or branched chain
C₁₋₈alkyl group(s); or a free carboxyl group;
or a carboxyl group esterified with a straight
or branched chain C₁₋₅ alcohol; and the
- 25 ---- bond line represents a single or double bond;
as well as their salts formed with pharmaceutically
acceptable bases when R¹ is a free carboxyl group.

The compounds of general formula (I) inhibit the
5 α -reductase enzyme and therefore, they block the
30 transformation of testosterone to dihydrotestosterone.
Thus, the compounds of general formula (I) are useful
for the healing of dihydrotestosterone-dependent
diseases, e.g. prostatic hyperplasia, acne vulgaris,
seborrhoea or female hirsutism.

35 According to literature references [European patent

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No. 4,949; as well as J. Med. Chem. 27, pages 1690 to 1701 (1984)] the preparation of the known compounds of general formula (I) can be accomplished in the manner described hereinafter.

5 After reacting pregnenolone (3 β -hydroxy-5-pregnen-20-one) with elemental iodine in pyridine, then the "21-pyridinium iodide" obtained is cleaved at the bond between C₂₀ and C₂₁ by using sodium methoxide to obtain the corresponding "17-carbomethoxy derivative". The
10 obtained 3 β -hydroxy-17 β -carbomethoxyandrost-5-ene is oxidized by aluminum isopropoxide in the presence of cyclohexanone in toluene, subsequently the carbomethoxy group is hydrolyzed to the carboxylic acid and transformed to the "17-carboxylic acid chloride" by
15 using oxalyl chloride. This acyl chloride is converted to e.g. "17 β -(N,N-diethylcarbamoyle)" derivative by using diethylamine. After oxidizing the thus obtained 17 β -(N,N-diethylcarbamoyle)androst-4-en-3-one to "seco acid" by using sodium periodate in tertiary butanol in
20 the presence of potassium permanganate, the seco compound is reacted with ammonia or an other primary amine in ethylene glycol to obtain e.g. 3-oxo-4-methyl-4-aza-androst-5-ene-17 β -(N,N-diethylcarboxamide). This latter substance is hydrogenated to the corresponding "4-aza-
25 -5 α -androstane" derivative in glacial acetic acid in the presence of hydrogen and platinum oxide catalyst. After isolation the final products are purified in various ways.

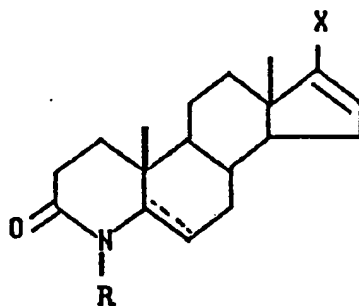
 The starting substance of the process described in
30 the literature is pregnenolone, which is obtained by hydrogenating the double bond in position 16 of pregnadienolone acetate obtained by the decomposition of diosgenin or solasodin of natural origin. However, the availability of pregnenolone is decreasing because the
35 Dioscorea species growing wild in Mexico is on the

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verge of dying off. The root of this plant is used for extracting diosgenin. On the other hand, the cultivation of *Solanum aviculare* and the isolation of solasodin therefrom are not economical according to our experience.

Considering their therapeutic activity, there exists a continuous demand on the target compounds in the pharmaceutical industry, however, this demand is more and more difficult to satisfy by using the known process of preparation because those discussed above.

The aim of the present invention is to develop a preparation process from a starting material which is easily available. From this point of view the new 17-halogeno-4-azaandrostene derivatives of general formula (II)



(II)

proved to be suitable.

Surprisingly, it has been found that a process completely satisfying the above demands for preparing the target compounds of general formula (I) can be accomplished by

reacting a 17-halogeno-4-azaandrostene derivative of general formula (II), wherein R and the ---- bond line are as defined above, and X is chlorine, bromine or iodine, with a primary or secondary alkylamine containing a C₁₋₈alkyl group or a straight or branched chain C₁₋₅ alcohol, respectively in dimethylformamide

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or dimethylsulfoxide medium in the presence of a palladium(II) salt and phosphines or a palladium(II) complex and a tertiary amine base in carbon monoxide atmosphere at a temperature between 35 °C and 80 °C,

5 then, if desired, hydrogenating a compound of general formula (I) containing a double bond as ---- bond line in the presence of a catalyst to obtain a compound of general formula (I) containing a single bond as ---- bond line, and/or

10 hydrolyzing in a known way a thus obtained compound of general formula (I) containing an esterified carboxyl group as R¹ to obtain a compound of general formula (I) containing a free carboxyl group as R¹, and/or

15 transforming a thus obtained compound of general formula (I) containing a free carboxyl group as R¹ to its salt by reacting it with a pharmaceutically acceptable base.

According to a preferred embodiment of the
20 invention a compound of general formula (II) is reacted with a primary or secondary amine in dimethylformamide in the presence of palladium(II) acetate, triphenylphosphine and triethylamine under carbon monoxide at 60 °C for 90 to 120 minutes. After the reaction has
25 become complete, the amines and dimethylformamide are distilled off under reduced pressure, the residue is dissolved in chloroform and successively washed with water, aqueous hydrochloric acid solution, aqueous sodium hydrogen carbonate solution and again with water
30 until neutral. After drying and evaporating the solvent, the residue is purified by chromatography or recrystallization or by using both methods.

If desired, the double bond [being in position 16 or in positions 5 and 16 depending on the starting
35 compound of general formula (II)] of the obtained

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compounds of general formula (I) containing a mono- or disubstituted carboxamido group as R^1 may be hydrogenated in the presence of gaseous hydrogen and charcoal supported palladium catalyst in formic acid or
5 in the presence of hydrogen and platinum oxide catalyst in glacial acetic acid.

For preparing compounds of general formula (I) containing an alkoxycarbonyl group as R^1 , a compound of general formula (II) is preferably reacted with a C_{1-5}
10 alkanol in dimethylsulfoxide, in the presence of a mixture of palladium(II) acetate, 1,4-bis(diphenylphosphino)butane and triethylamine under carbon monoxide at 60 °C for 10 to 15 hours. After the reaction has become complete, the volatile components
15 are distilled off under reduced pressure, the residue is dissolved in chloroform and the water-soluble components are removed by washing with water. After drying the solution and evaporating the solvent, the residue is purified by chromatography or recrystalliza-
20 tion or by using both methods.

If desired, the obtained compound of general formula (I) is hydrogenated as described above, i.e. in formic acid in the presence of hydrogen and charcoal supported palladium or in glacial acetic acid in the
25 presence of hydrogen and platinum oxide as catalyst and/or optionally hydrolyzed to the corresponding 17 β -carboxylic acid derivative in alkaline medium.

In the process according to the invention 1,4-bis(diphenylphosphino)butane, 1,2-bis(diphenylphosphino)-
30 ethane, triphenylphosphine or 1,3-bis(diphenylphosphino)propane is preferably used as a phosphine although a complex of the above phosphines with palladium(II) salts may also be employed: e.g. the reaction is carried out at 35 to 60 °C with primary or
35 secondary amines and at 40 to 80 °C with C_{1-5} alcohols

in the presence of bis(triphenylphosphino)palladium(II) dichloride.

The process according to the invention provides the use of the easily available 3-keto- Δ^4 derivatives as starting substances, which can be obtained by the decomposition of sitosterin. According to the invention the building-up of the 17-carboxamido or 17-carboalkoxy group, respectively can safely be carried out and the scale increase of the process needed for the industrial utilization is not burdened by any problem.

The starting substances used in the process according to the invention such as "4-aza-17-hydrazone" derivatives as well as the compounds of general formula (II) are new. Similarly, the unsaturated 4-aza-17-carboxamido- as well as 4-aza-17-alkoxycarbonyl derivatives of general formula (I) are also novel compounds. The saturated 4-aza-17-carboxamido derivatives as well as the saturated 4-aza-17-methoxycarbonyl derivative are known from the literature [European patent No. 4,949; J. Med. Chem. 27, pages 1690 to 1701 (1984)].

The novel 17-halogeno-4-azaandrostene derivatives of general formula (II) used as starting substances in the process of the present invention can be prepared as follows.

4-Aza-5 α -androstane-3,17-dione, 4-methyl-4-aza-androstane-3,17-dione as well as 4-azaandrost-5-ene-3,17-dione (hereinafter named as 4-aza-17-keto derivatives), which are known compounds, can be prepared by a process described in the literature [J. Pharm. Sci. 63, pages 19 to 23 (1974); J. Med. Chem. 27, pages 1690 to 1701 (1984); J. Org. Chem. 46, pages 1442 to 1446 (1981)] from the known 17 β -hydroxy-androst-4-en-3-one.

The known "4-aza-17-keto derivatives" are reacted with hydrazine hydrate in ethanol in the presence of

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triethylamine, after working up the reaction mixture (carried out as described in Example 1) the "hydrazone derivatives" formed are isolated and the crude products
5 are immediately used without any purification for preparing the 17-halogeno-4-azaandrostene derivatives of general formula (II) as described hereinafter.

For the preparation of 17-iodo-4-azaandrostene derivatives the "hydrazone derivatives" are dissolved in chloroform or benzene or in a mixture thereof or in
10 tetrahydrofuran and then reacted with elemental iodine in the presence of a tertiary amine base at room temperature. After complete reaction the compounds of general formula (II) are obtained as described in Example 4.

15 For the preparation of 17-halogeno-4-azaandrostene derivatives containing chlorine or bromine in position 17, the "hydrazone derivatives" are dissolved in pyridine optionally substituted by C₁₋₄alkyl group and reacted with N-chloro or N-bromosuccinimide, respectively
20 at a temperature between -10 °C and +10 °C. The resulted compound of general formula (II) is isolated as described in Example 7.

The process according to the invention is illustrated in detail by the following non-limiting
25 Examples.

Example 1

Preparation of 17-hydrazono-4-aza-5 α -androstan-3-one

30 To a suspension containing 10 g (0.0346 mol) of 4-aza-5 α -androstan-3,17-dione in 100 ml of ethanol 14 ml (0.1 mol) of triethylamine and 50 ml (1.0 mol) of hydrazine hydrate are added and the mixture is boiled under reflux for 3 hours. (The progress of the reaction
35 is followed by thin layer chromatography.) After the

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reaction has become complete the reaction mixture is cooled down, the solution is evaporated to one tenth of its original volume and the product is precipitated by adding about a 10-fold volume of water. After compaction the precipitate is filtered, washed with water until neutral and dried to obtain the title compound. Yield: 9.44 g (90%), m.p.: 254-258 °C.

¹H-NMR (300 MHz, CDCl₃) δ ppm: 0.86 (s, 3H, 18-CH₃), 0.93 (s, 3H, 19-CH₃), 2.41 (m, 2H, H-2), 3.07 (dd, 1H, H-5), 4.77 (br, 2H, NH₂), 5.74 (br, 1H, NH).

Example 2

Preparation of 17-hydrazono-4-azaandrost-5-en-3-one

The process described in Example 1 is followed, except that 4-azaandrost-5-ene-3,17-dione is used as starting substance to obtain the title compound.

Yield: 35%, m.p.: 379-382 °C.

IR (KBr) ν : 1633 (C=C), 1661 (C=N), 1693 (C=O), 3200 (NH), 3350 (NH₂) cm⁻¹.

Example 3

Preparation of 17-hydrazono-4-methyl-4-aza-5 α -androstan-3-one

The process described in Example 1 is followed, except that 4-methyl-4-aza-5 α -androstan-3,17-dione is used as starting substance to give the title compound.

Yield: 75%, m.p.: 211-218 °C.

¹H-NMR (300 MHz, CDCl₃) δ ppm: 0.86 (s, 3H, 18-CH₃), 0.91 (s, 3H, 19-CH₃), 2.93 (s, 3H, N-CH₃), 3.05 [dd(J=3.6; J=12.6), 1H, H-5], 4.78 (v br, 2H, NH₂).

Example 4**Preparation of 17-iodo-4-aza-5 α -androsta-16-en-3-one**

After dissolving 9.1 g (0.03 mol) of 17-hydrazono-4-
5 -aza-5 α -androsta-3-one in 1200 ml of an 1:1
chloroform/benzene mixture and adding 90 ml of tri-
ethylamine, 11.4 g (0.045 mol) of iodine dissolved in
110 ml of benzene are dropwise added to the above
solution. The reaction mixture is stirred at room
10 temperature for additional 60-90 minutes. (The progress
of the reaction is followed by thin layer
chromatography). After complete occurrence of the reac-
tion the obtained solution is diluted with 500 ml of
chloroform and successively washed with 10% aqueous
15 hydrochloric acid solution, water, 5% aqueous sodium
thiosulfate solution, water, 5% aqueous sodium hydrogen
carbonate solution, finally with water and dried over
anhydrous sodium sulfate. After evaporating the
solvents under reduced pressure the residue is purified
20 by chromatography on a silica gel column by using first
chloroform and subsequently a 95:5 chloroform/acetone
mixture as eluents. The product obtained is re-
crystallized from ethanol to give the title compound.
Yield: 5.9 g (50%), m.p.: 278-282 °C.
25 ¹H-NMR (300 MHz, CDCl₃) δ ppm: 0.73 (s, 3H, 18-CH₃),
0.91 (s, 3H, 19-CH₃), 3.1 (dd, 1H, H-5), 6.18
(m, 1H, H-16), 6.9 (br, 1H, NH).

Example 5**30 Preparation of 17-iodo-4-azaandrosta-5,16-dien-3-one**

The process described in Example 4 is followed,
except that 17-hydrazono-4-azaandrosta-5-en-3-one is
used as starting substance to obtain the title com-
35 pound. Yield: 57%, m.p.: 227-230 °C.

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¹H-NMR (300 MHz, CDCl₃) δ ppm: 0.78 (s, 3H, 18-CH₃), 1.13 (s, 3H, 19-CH₃), 4.9 [dd(J=2.4; J=5.1), 1H, H-6], 6.15 [dd(J=3.2; J=1.7), 1H, H-16], 8.27 (br, 1H, NH).

5 **Example 6**

Preparation of 17-iodo-4-methyl-4-aza-5α-androst-16-en-3-one

The process described in Example 4 is followed, except
10 that 17-hydrazono-4-methyl-4-aza-5α-androstan-3-one is used as starting substance and the reaction is carried out in benzene. The title compound is obtained in a yield of 52%, m.p.: 176-181 °C.

¹H-NMR (300 MHz, CDCl₃) δ ppm: 0.74 (s, 3H, 18-CH₃),
15 0.92 (s, 3H, 19-CH₃), 2.94 (s, 3H, N-CH₃), 3.07 [dd(J=3.7; J=12.6), 1H, H-5], 6.13 [dd(J=3.2; J=1.7), 1H, H-16].

Example 7

20 **Preparation of 17-chloro-4-methyl-4-aza-5α-androst-16-en-3-one**

A solution containing 4 g (0.0126 mol) of 17-hydrazono-4-methyl-4-aza-5α-androstan-3-one in 40 ml
25 of anhydrous pyridine is cooled to 0 °C and the solution of 3.2 g (0.024 mol) of N-chlorosuccinimide in 40 ml of pyridine is dropwise added under vigorous stirring. After cessation of the violent nitrogen gas evolution the reaction mixture is stirred for
30 additional 15 minutes and then dropped to 800 ml of water. After compaction of the precipitate the crude product is filtered, washed with water until neutral and dried over phosphorus pentoxide under reduced pressure at room temperature. The crude product
35 obtained is purified by chromatography on a silica gel

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column by using chloroform as eluent. After recrystallization of the evaporation residue from petroleum ether the title compound is obtained in a yield of 2.15 g (53%), m.p.: 139-140 °C.

- 5 ¹H-NMR (300 MHz, CDCl₃) δ ppm: 0.88 (s, 3H, 18-CH₃),
0.93 (s, 3H, 19-CH₃), 2.89 (s, 3H, N-CH₃), 3.0
(dd, 1H, H-5), 5.53 (m, 1H, H-16).

Example 8

- 10 Preparation of 17-bromo-4-methyl-4-aza-5α-androst-16-en-3-one

The process described in Example 7 is followed by using 17-hydrazono-4-methyl-4-aza-5α-androstan-3-one as
15 starting substance and N-bromosuccinimide as reactant to give the title compound. Yield: 55%, m.p.: 159-161 °C.

- ¹H-NMR (300 MHz, CDCl₃) δ ppm: 0.82 (s, 3H, 18-CH₃),
0.91 (s, 3H, 19-CH₃), 2.86 (s, 3H, N-CH₃), 3.0
20 (dd, 1H, H-5), 5.68 (m, 1H, H-16).

Example 9

Preparation of 3-oxo-4-aza-5α-androst-16-ene-17β-(N-tert-butylcarboxamide)

25

- To a solution containing 3.99 g (0.01 mol) of 17-iodo-4-aza-5α-androst-16-en-3-one in 150 ml of dimethylformamide, 0.224 g (0.001 mol) of palladium(II) acetate, 0.524 g (0.002 mol) of triphenylphosphine,
30 10 ml of triethylamine and 15 ml (0.14 mol) of tert-butylamine are added and the mixture is heated at 60 °C under carbon monoxide for 90 to 120 minutes. (The progress of the reaction is followed by thin layer and gas chromatography.) After the reaction has become
35 complete the amines and dimethylformamide are distilled

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off under reduced pressure, then the residue is dissolved in 150 ml of chloroform and successively washed with water, 5% aqueous hydrochloric acid solution, saturated aqueous sodium hydrogen carbonate solution and saturated aqueous sodium chloride solution until neutral and finally dried over anhydrous sodium sulfate. After evaporating the solvent the residue is purified by chromatography on a silica gel column by using ethyl acetate as eluent to obtain the title compound. Yield: 3.16 g (85%), m.p.: 292-297 °C.

¹H-NMR (300 MHz, CDCl₃) δ ppm: 0.93 (s, 3H, 19-CH₃), 1.0 (s, 3H, 18-CH₃), 1.4 (s, 3H, C(CH₃)₃), 2.15 (m, 2H, H-15a+H-15b), 2.4 (m, 2H, H-2), 3.08 [dd (J=4.5; J=7.0), 1H, H-5], 5.48 (br s, 1H, NH), 5.6 (br s, 1H, NH), 6.18 [dd (J=1.7; J=1.4), 1H, H-16].

Example 10

Preparation of 3-oxo-4-aza-5α-androst-16-ene-17β-[N-(2,2-dimethylpropyl)carboxamide]

20

The process described in Example 9 is followed by using 17-iodo-4-aza-5α-androst-16-en-3-one as starting substance and 2,2-dimethylpropylamine (neopentylamine) as reactant to obtain the title compound. Yield: 82%.

¹H-NMR (300 MHz, CDCl₃) δ ppm: 0.92 (s, 9H, C(CH₃)₃), 0.95 (s, 3H, 19-CH₃), 1.02 (s, 3H, 18-CH₃), 2.4 (m, 2H, H-2), 3.1 (m, 3H, NCH₂, H-5), 5.66 (br s, 1H, NH), 5.85 (br s, 1H, NH), 6.3 (br s, 1H, H-16).

Example 11

Preparation of 4-methyl-3-oxo-4-aza-5α-androst-16-ene-17-carboxylic acid methyl ester

A mixture containing 0.41 g (0.001 mol) of 17-iodo-4-methyl-4-aza-5α-androst-16-en-3-one, 0.0224 g

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(0.1 mmol) of palladium(II) acetate, 0.0213 g
(0.05 mmol) of 1,4-bis(diphenylphosphino)butane, 0.3 ml
of triethylamine, 2 ml of methanol and 15 ml of di-
methylsulfoxide is stirred under carbon monoxide at
5 60 °C for 10 to 15 hours: (The progress of the reaction
is followed by thin layer and gas chromatography.)
After complete reaction the mixture is evaporated under
reduced pressure, the residue is dissolved in 15 ml of
chloroform, the chloroform solution is washed 4 times
10 with water and dried over anhydrous sodium sulfate.
After evaporation of the solvent the residue is
purified by chromatography on a silica gel column by
using an 1:10 mixture of ethyl acetate/petroleum ether
as eluent. The title compound is obtained in a yield of
15 0.014 g (40%), m.p.: 182-186 °C.

¹H-NMR (300 MHz, CDCl₃) δ ppm: 0.93 (s, 6H, 18-CH₃ +
+ 19-CH₃), 2.45 (m, 2H, H-2), 2.94 (s, 3H, NCH₃), 3.07
(dd, 1H, H-5), 3.72 (s, 3H, OCH₃), 6.76 (br s, 1H, H-16).

20 Example 12

Preparation of 3-oxo-4-aza-5 α -androst-16-ene-17- carboxylic acid methyl ester

The process described in Example 11 is followed by
25 using 17-iodo-4-aza-5 α -androst-16-en-3-one as starting
substance to give the title compound. Yield: 42%,
m.p.: 270 °C.

¹H-NMR (300 MHz, CDCl₃) δ ppm: 0.92 (s, 3H, 19-CH₃),
0.94 (s, 3H, 18-CH₃), 2.4 (m, 2H, H-2), 3.07
30 (dd, 1H, H-5), 3.72 (s, 3H, OCH₃), 6.15 (br s, 1H, NH),
6.75 (br s, 1H, H-16).

Example 13

Preparation of 3-oxo-4-azaandrosta-5,16-diene-17 β -(N-tert-butylcarboxamide)

5 The process described in Example 9 is followed by using 17-iodo-4-azaandrosta-5,16-dien-3-one as starting substance and tert-butylamine as reactant to give the title compound. Yield: 78%, m.p.: 266-269 °C.

10 ¹H-NMR (300 MHz, CDCl₃) δ ppm: 1.04 (s, 3H, 18-CH₃),
1.14 (s, 3H, 19-CH₃), 1.38 (s, 9H, C(CH₃)₃), 2.5
(m, 2H, H-2), 4.88 [dd (J=2.1; J=2.7), 1H, H-6], 5.5
(br s, 1H, NH), 6.2 [dd (J=1.8; J=0.9), 1H, H-16],
8.08 (br s, 1H, NH).

15 **Example 14**

Preparation of 4-methyl-3-oxo-4-aza-5 α -androst-16-ene-17 β -(N,N-diethylcarboxamide)

a.)

20 The process described in Example 9 is followed by using 17-iodo-4-methyl-4-aza-5 α -androst-16-en-3-one as starting substance and diethylamine as reactant. In this way the title compound is obtained in a yield of 84%, m.p.: 205-210 °C.

25 ¹H-NMR (300 MHz, CDCl₃) δ ppm: 0.93 (s, 3H, 19-CH₃),
1.09 (s, 3H, 18-CH₃), 1.13 (t, 6H, N(CH₂CH₃)₂), 2.94
(s, 3H, NCH₃), 3.06 (dd, 1H, H-5), 5.26 (m, 1H, H-16).

b.)

30 The process described in Example 9 is followed by using 17-bromo-4-methyl-4-aza-5 α -androst-16-en-3-one as starting substance and diethylamine as reactant. In this way the title compound is obtained in a yield of 85%, m.p.: 205-210 °C.

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Example 15**Preparation of 4-methyl-3-oxo-4-aza-5 α -androstane-17 β -
-(N,N-diethylcarboxamide)**

5 A suspension containing 1 g of charcoal supported
palladium catalyst in 6 ml of water is added to the
solution of 1 g (2.6 mmol) of 4-methyl-3-oxo-4-aza-5 α -
-androst-16-ene-17 β -(N,N-diethylcarboxamide) in 40 ml
of formic acid under nitrogen. The heterogeneous
10 mixture is stirred at room temperature for 4 to 5 hours
while observing the progress of the reduction by thin
layer chromatography. After the reaction has become
complete the catalyst is filtered off and washed with
an 1:1 mixture of chloroform/methanol. After evaporat-
15 ing the combined solution to dryness the evaporation
residue is thoroughly triturated with water, the
precipitate is filtered and washed with water to
obtain the title compound. Yield: 0.88 g (87%), m.p.:
180-181 °C (after recrystallization from ethyl
20 acetate).

Example 16**Preparation of 3-oxo-4-aza-5 α -androstane-17 β -(N-tert-
-butylcarboxamide)**

25

The process described in Example 15 is followed by
using 3-oxo-4-aza-5 α -androst-16-ene-17 β -(N-tert-butyl-
carboxamide) as starting substance to obtain the title
compound. Yield: 90%, m.p.: 283-286 °C.

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Example 17

Preparation of 3-oxo-4-aza-5 α -androstane-17 β -carboxylic acid methyl ester

- 5 The process described in Example 15 is followed by using 3-oxo-4-aza-5-androst-16-ene-17-carboxylic acid methyl ester as starting substance to give the title compound. Yield: 85%, m.p.: 301-304 °C (after recrystallization from ethyl acetate).

10

Example 18

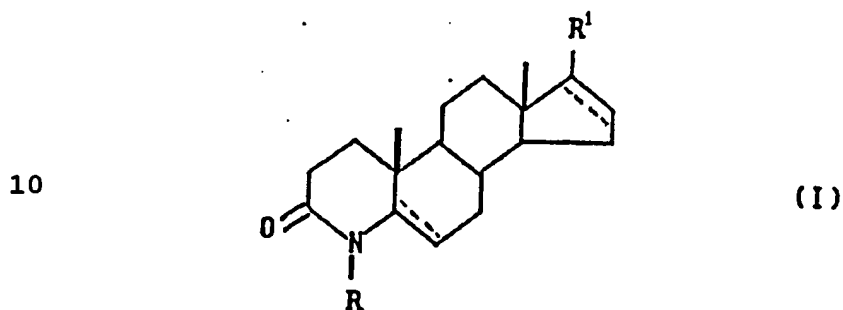
Preparation of 3-oxo-4-aza-5 α -androstane-17 β -(N-tert-butylcarboxamide)

- 15 The process described in Example 15 is followed by using 3-oxo-4-azaandrost-5,16-ene-17 β -(N-tert-butylcarboxamide) as starting substance to obtain the title compound. Yield: 70%, m.p.: 283-286 °C.

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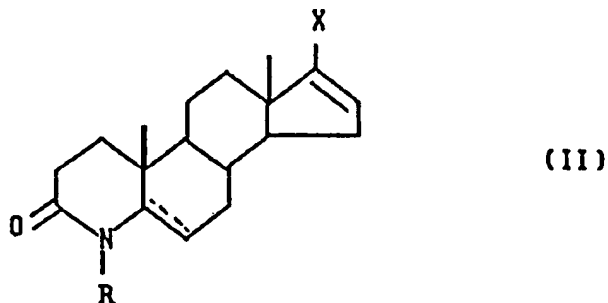
Claims

1. A process for the preparation of 17 β -substituted 4-azaandrostane derivatives of the general
 5 formula (I),



15 wherein

- R represents hydrogen or a C₁₋₃alkyl group;
 R¹ represents a carboxamido group mono- or
 disubstituted by straight or branched chain
 C₁₋₈alkyl group(s); or a free carboxyl group;
 20 or a carboxyl group esterified with a straight
 or branched chain C₁₋₅ alcohol; and the
 ---- bond line represents a single or double bond;
 as well as their salts formed with pharmaceutically
 acceptable bases when R¹ is a free carboxyl group,
 25 which comprises,
 reacting a 17-halogeno-4-azaandrostene derivative
 of general formula (II),



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- wherein R and the ---- bond line are as defined above,
and X is chlorine, bromine or iodine, with a primary or
secondary alkylamine containing a C₁₋₈alkyl group or a
straight or branched chain C₁₋₅ alcohol, respectively
5 in dimethylformamide or dimethylsulfoxide medium in
the presence of a palladium(II) salt and phosphines or
a palladium(II) complex and a tertiary amine base in
carbon monoxide atmosphere at a temperature between
35 °C and 80 °C,
- 10 then, if desired, hydrogenating an obtained com-
pound of general formula (I) containing a double bond
as ---- bond line, wherein R and R¹ are as defined
for the general formula (I), in the presence of a
catalyst to obtain a compound of general formula (I)
15 containing a single bond as ---- bond line, wherein R
and R¹ are as defined for the general formula (I),
and/or
- hydrolyzing in a known way a thus obtained compound
of general formula (I) containing an esterified
20 carboxyl group as R¹, wherein R and the ---- bond line
are as defined for the general formula (I), to obtain a
compound of general formula (I) containing a free
carboxyl group as R¹, wherein R and the ---- bond line
are as defined for the general formula (I), and/or
- 25 transforming a thus obtained compound of general
formula (I), wherein R and the ---- bond line are as
defined for the general formula (I) and R¹ is a free
carboxyl group, to its salt by reacting it with a
pharmaceutically acceptable base.
- 30 2. A process as claimed in claim 1, which
c o m p r i s e s using triethylamine as a tertiary
amine base.
3. A process as claimed in claim 1 or claim 2,
which c o m p r i s e s, using palladium(II)
35 acetate or palladium(II) chloride as palladium(II)

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salt.

4. A process as claimed in any of the claims 1 to 3, which comprises using triphenylphosphine, 1,4-bis(diphenylphosphino)butane, 1,2-bis-
5 (diphenylphosphino)ethane or 1,3-bis(diphenylphosphino)propane as phosphine.

5. A process as claimed in claim 1 or claim 2, which comprises using bis(triphenylphosphino)palladium(II) dichloride or diacetate as
10 palladium(II) complex.

6. A process as claimed in any of the claims 1 to 5, which comprises carrying out the amidation or alkoxycarbonylation reaction at a temperature of 50 to 60 °C.

15 7. A process as claimed in any of the claims 1 to 6, which comprises carrying out the saturation of the double bonds in the presence of a palladium or platinum catalyst.

8. A process as claimed in claim 7, which
20 comprises carrying out the hydrogenation in glacial acetic acid or formic acid medium.

9. A process as claimed in any of the claims 1 to 8 for the preparation of compounds of the general formula (I) containing an N,N-diethylcarboxamido, N-
25 -tert-butylcarboxamido or N-(2,2-dimethylpropyl)carboxamido group as R¹, which comprises using diethylamine, tertiary butylamine or 2,2-dimethylpropylamine, respectively as an alkylamine.

10. A process as claimed in any of the claims 1 to
30 8 for the preparation of compounds of the general formula (I) containing a methoxycarbonyl group as R¹, which comprises using methanol as an alcohol.

11. A process for the preparation of a pharmaceutical composition inhibiting the 5 α -reductase
35

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enzyme, which c o m p r i s e s mixing as active ingredient one or more 17 β -substituted 4-azaandrostande derivative(s) of the general formula (I), wherein R, R¹ and the ---- bond line are as defined in claim 1 and/or
5 salt(s) of this (these) compound(s) formed with pharmaceutically acceptable base(s), prepared by using the process claimed in any of the claims 1 to 10, with filling, diluting, stabilizing, pH- and osmotic pressure-adjusting and/or formulation-promoting auxiliaries
10 and transforming them to a pharmaceutical composition.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/HU 93/00039

A. CLASSIFICATION OF SUBJECT MATTER

IPC⁵: C 07 J 73/00, A 61 K 31/58

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC⁵: C 07 J 73/00, A 61 K 31/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	EP, A2, 0 473 225 (MERCK & CO) 04 March 1992 (04.03.92), claims 1-5.	1

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

11 February 1994 (11.02.94)

Date of mailing of the international search report

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Name and mailing address of the ISA/ AT
 AUSTRIAN PATENT OFFICE
 Kohlmarkt 8-10
 A-1014 Vienna
 Facsimile No. 1/53424/535

Authorized officer

Hofbauer e.h.

Telephone No. 1/5337058/26

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/HU 93/00039

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